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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/630,383	04/10/96	POULETTY	P A-55320-2/BI

HM22/1005
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EXAMINER	
SCHWADRON, R	
ART UNIT	PAPER NUMBER
1644	32

DATE MAILED: 10/05/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applic[illegible]
08/630,383	Pouletty et al.
Examiner: Ron Schwadron, Ph.D.	Art Unit: 1644

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1, 2, 4, and 6-8* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideratio

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1, 2, 4, 6-8 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some* c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15)☐ Notice of References Cited (PTO-892)

16)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____

18)☐ Interview Summary (PTO-413) Paper No(s). _____

19)☐ Notice of Informal Patent Application (PTO-152)

20)☐ Other:

1. Claims 1,2,4,6-8 are under consideration. Claims 3,5,9-11,13 have been cancelled.

RESPONSE TO APPLICANTS ARGUMENTS

2. References not considered in the IDS filed 8/29/2001 were already of record on a previously filed IDS.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1,2,4,6-8 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for the reasons elaborated in the previous Office action. Applicants arguments have been considered and deemed not persuasive.

The specification does not disclose how to use the instant invention for the treatment of disease in vivo in humans. It appears that undue experimentation would be required of one skilled in the art to practice the instant invention using the teaching of the specification alone. See Ex parte Forman, 230 USPQ 546, BPAI, 1986. Regarding applicants comments, the following comments are made. The claims of the instant invention read on a method that the specification discloses can be used for the treatment of human disease in vivo. Applicant has not enabled the breadth of the claimed invention in view of the teachings of the specification because the claims encompass a method for human therapy.

The state of the art is such that is unpredictable from the in vitro or in vivo mouse data disclosed in the specification as to whether (and how) the instant invention could be used for the

treatment of disease in vivo in humans. Applicants comments regarding *Ex Parte Kranz* on pages 9-10 of the instant amendment are also noted in that applicant appears to be arguing that the specification needs to provide actual working examples of the scope of the claimed invention.

Regarding the various filed Lussow et al. papers the following comments are made. The various Lussow et al. papers disclose use of a particular construct (eg. FITC/Il-2). None of the instant claims recite use of said conjugate or are restricted to use of such a conjugate. Lussow et al. (Transplantation) disclose that the conjugate used must be nonimmunogenic and of low molecular weight (see abstract). None of the instant claims recite use of said conjugate or are restricted to use of such a conjugate. Furthermore, Lussow et al. (Transplantation) disclose that a potential difficulty regarding the use of the instant conjugate is that it can be eliminated from the immune system (see page 1703). The Lussow et al. references and experiments disclosed in the specification are drawn to experiments using rodents and do not provide evidence that the aforementioned problems would not arise when the claimed method was used in humans. There is also no evidence of record that establishes that the mouse pharmacokinetic response to the conjugate would be the same as humans. Borrebaeck et al. establish that there are clear pharmacokinetic differences in the halflife of murine antibodies administered to mice versus humans, in that murine antibodies administered to humans have greatly reduced halflife in comparison to human antibodies (see column 1, page 477). Therefore a xenogeneic conjugate administered to a human would not necessarily have the same pharmacokinetic properties as when said conjugate was administered to a human. The Borrebaeck et al. reference establishes that conjugates containing α gal would be subjected to an anti-α gal response (that can neutralize the conjugate), wherein such a response would not occur in mice because anti-α gal antibodies are not found in mice.

Regarding applicants comments about the state of the art and the various cited references supplied in the IDS filed 8/29/2001, as per applicants comments in page 6 of the instant amendment, last paragraph, the claimed invention does not use antibody conjugates so therefore the various cited references related to use of antibody conjugates are not germane to the claimed invention. The claimed inventions also do not encompass use of immunotoxins.

Regarding the mouse data disclosed in page 23 of the specification, said experiments relate to the lysis of normal cells and provides no evidence that the instant invention can be used for the

treatment of any mouse disease. Regarding the mouse allograft data disclosed in page 30 of the specification, it is well known in the art that rodent models for the study of transplantation do not produce results that are readily applicable to humans and are therefore not predictive of whether particular agents can be used in vivo for the treatment of transplantation rejection in humans. Tueveson et al. teach that one problem with rodent models of transplantation is that rejection is easily overcome in said models in comparison to the difficulty of overcoming allograft rejection in humans (see page 100, first full paragraph). Tueveson et al. also teach that, "However, today's small animal models seem to be insufficient to produce data for clinical decision-making." (page 101, second paragraph). Osband et al. teaches that the response of animals to immunotherapy is not predictive of the response in humans(see page 193, second column, first paragraph). The data disclosed in page 30 of the specification provides no evidence that naturally occurring endogenous antibodies (eg. autoantibodies, antibodies against xenoantigens), which are encompassed by the claims of the instant invention, can function as an effector mechanism in the claimed invention. Borrebaeck et al. teach that naturally occurring antibodies against xenoantigens(eg. anti α gal antibodies) do not function as an endogenous effector system as per the claimed method, for the reasons stated below (see comments about Borrebaeck et al.). The evidence of record has also provided no working examples demonstrating that the conjugates used in the method of the instant invention can used to reduce the concentration of a soluble target molecule.

Regarding the Soulillou declaration filed 3/31/97, no copy of Soulillou's curriculum vitae was submitted with the instant declaration, therefore, it is unclear as to whether Dr. Soulillou is an expert in the field of immunology. Furthermore, the Soulillou declaration provides no experimental evidence which establishes that the rodent models for the study of transplantation produce results that are readily applicable to humans and are therefore predictive of whether particular agents can be used in vivo for the treatment of transplantation rejection in humans. Tueveson et al. teach that one problem with rodent models of transplantation is that rejection is easily overcome in said models in comparison to the difficulty of overcoming allograft rejection in humans. The Soulillou declaration filed 3/31/97 does not provide any evidence that contradicts the aforementioned problem noted by Tueveson with regards to rodent models for transplantation. In fact, Soulillou seems to indicate that Tuevson et al. are correct in stating that there is no direct correlation between the rodent model and applicability to human use (eg. see first complete paragraph). The issue at hand is not whether the rodent model is used to screen for immunosuppressive drugs, but whether the rodent model is predictive in itself of whether an agent

can be used in vivo for the treatment of human disease. Regarding Soulillou's comments on page 2, the murine and human immune systems differ in many ways. For example, the human immune system contains anti- α gal antibodies are not found in rodents and which can neutralize the efficacy of rodent antibodies. Regarding applicants comments about the Tuevson et al. publication, no actual evidence has been presented in the Soulillou declaration which refutes the statements made by Tuevson et al. Regarding comments about in the Soulillou declaration about Borrebaeck et al., Borrebaeck et al. teach that murine antibodies often contain the α gal antigen (see page 477). Borrebaeck et al. teach that naturally occurring anti-α gal antibodies are found in humans and that said antibodies bind murine monoclonal antibodies when said murine monoclonal antibodies are administered to humans (see page 477, third column first complete paragraph). Borrebaeck et al. teach that , "The presence of anti-Gal antibodies in human serum ensures a quick removal of the xenogeneic mouse mAbs, containing Galα 1-3Gal residues, which results in a lack of antibody mediated effect on neoplastic target cells"(see page 477, third column first complete paragraph). It appears that conjugates containing α gal antigen would also suffer a similar fate and therefore also not be available to mediate lysis of a target cell. Borrebaeck et al. also teaches that the binding of anti-α gal antibodies interferes with the immune function of murine monoclonal antibodies without resulting in any effector function as a consequence of the bound anti α gal antibodies (see page 477, third column, first complete paragraph, last sentence). The teachings of Borrebaeck et al. seem to indicate that the preformed antibodies (eg. endogenous antibodies) do not act as an immunologic effector system upon binding of said antibodies to an exogenously administered agent , but instead result in the removal of said agent thus preventing the agent from reaching the appropriate target cell. The Soulillou declaration has provided no actual evidence that contradicts the statement made by Borrebaeck et al.

Regarding applicants comments, the claims of the instant invention do not specify that the target is T cells involved in transplantation rejection. The claims read on a method where the target could be a T cell lymphoma which expresses IL-2 receptors. In such a scenario, normal T cells capable of mediating killing would also express the IL-2 receptor, and therefore the aforementioned conjugate would bind to normal T cells and not be available to bind a target cell. Furthermore, the killing of normal T cells would leave tumor bearing patient immunocompromised without necessarily having any effect on the T cell lymphoma. This would also apply to many cytokines, whose receptors are also found on T cells (such as IL-4, IL-6, IL-

10, etc.).It is unclear as to how the method of the instant invention can inactivate target cells without also inactivating normal cells that express receptors for said cytokine. If the target cell population is present in lesser numbers compared to normal cells which express the relevant cytokine receptor it is also unclear as to whether sufficient quantities of said conjugate would be present to react with a target cell population after interaction with normal cells that possess the pertinent cytokine receptor. Regarding applicants comments, there is no limitation in the claims that specifies that the target cell population has a surface membrane receptor that is upregulated in a particular population but not normal cells.

In addition, there is no guidance in the specification as to how to determine the dosage of conjugate to use for treatment of a particular disease. It is therefore unclear as to whether the dosages used in said experiment could be used for the treatment of disease, because no disease was actually treated in said experiment. There is also no evidence of record that establishes that the mouse pharmacokinetic response to the conjugate would be the same as humans. Borrebaeck et al. establish that there are clear pharmacokinetic differences in the halflife of murine antibodies administered to mice versus humans, in that murine antibodies administered to humans have greatly reduced halflife in comparison to human antibodies (see column 1, page 477). Therefore a xenogeneic conjugate administered to a human would not necessarily have the same pharmacokinetic properties as when said conjugate was administered to a human. The Borrebaeck et al. reference establishes that conjugates containing α gal would be subjected to an anti-α gal response (that can neutralize the conjugate), wherein such a response would not occur in mice because anti-α gal antibodies are not found in mice. There is also no guidance in the specification as to how to determine if an appropriate level of endogenous antibody (eg. endogenous cytotoxic effector) is present so that target cell lysis could be effected by the administered conjugate.

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 1,2,6 stand rejected under 35 U.S.C. § 102(b) as being clearly anticipated by Pouletty (EP 0510949) for the reasons elaborated in the previous Office action. Applicants arguments have been considered and deemed not persuasive.

Regarding applicants comments, the Board of Appeals upheld the rejection of claims filed in 07/690530 as not enabled under 35 USC 112 first paragraph for the reasons disclosed in the Board decision mailed 9/30/99. Therefore, the claimed invention is not entitled to priority to parent application 07/690530 because the claimed invention was not enabled in said application. Regarding applicants comments in page 8, last two paragraphs of the instant amendment, in paragraph 3, applicant argues that Pouletty is enabled, while in paragraph 4, applicant argues that Pouletty is not enabled.

In addition, regarding the limitation of claim 6, there is no disclosure in parent application 07/690530 of use of a "small organic molecule having a molcular weight of more than 100 and less than about 5000 daltons". Regarding applicants comments about page 4, lines 1-22 of 07/690530, said passage does not disclose a "small organic molecule having a molcular weight of more than 100 and less than about 5000 daltons" or the scope of said phrase. Applicant appears to be arguing that the limitation is obvious in view of a specific example disclosed in the specification, even though specific example does not provide written description of the scope of the claimed invention. However, obviousness is not the appropriate standard with regards to issues of written description. The CAFC stated in Lockwood v. American Airlines Inc., 41 USPQ2d 1961 (Fed. Cir. 1997) that:

3. Patentability/Validity -- Specification -- Written description (§ 115.1103)
Patent's entitlement to earlier filing date extends only to that which is disclosed in prior application, and does not extend to subject matter which is not disclosed, but would be obvious over what is expressly disclosed; one shows that one is "in possession" of invention of patent by describing invention, with all its claimed limitations, not that which makes it obvious, and although prior application need not describe claimed subject matter in exactly same terms used in claims, prior specification must contain equivalent description of claimed subject matter, and description which renders obvious invention for which earlier filing date is sought is not sufficient.

The CAFC also stated in Lockwood v. American Airlines Inc., 41 USPQ2d 1961 (Fed. Cir. 1977) that:

The invention is, for purposes of the 'written description' inquiry, whatever is now

claimed .") (emphasis in original). One does that by such descriptive means as words, structures, figures, diagrams, formulas, etc., that fully set forth the claimed invention. Although the exact terms need not be used in haec verba , see Eiselstein v. Frank , 52 F.3d 1035, 1038, 34 USPQ2d 1467, 1470 (Fed. Cir. 1995) (" [T]he prior application need not describe the claimed subject matter in exactly the same terms as used in the claims.. . . "), the specification must contain an equivalent description of the claimed subject matter. A description which renders obvious the invention for which an earlier filing date is sought is not sufficient.

7. Claim 1 stands rejected under 35 U.S.C. § 102(b) as being clearly anticipated by Kranz et al. (EP 0180171) for the reasons elaborated in the previous Office action. Applicants arguments have been considered and deemed not persuasive.

Regarding applicants comments about Kranz et al., Kranz et al. disclose the claimed method for lysing target cells wherein the conjugate used does not use an antibody as the "moiety specific for a surface protein" (see abstract and claims). Kranz et al. disclose use of a conjugate containing a growth factor as the "moiety specific for a surface protein" (see claims 27-31) and a "selective moiety" which is an antiT3 antibody (which binds the TCR). The claims under consideration do not exclude of an antibody as the "selective Moe". Kranz et al. disclose the claimed method is used in vivo wherein lysis is mediated by T cells which bind said conjugate wherein the conjugate is bound by the appropriate target cell (see pages 3 and 4).

Regarding applicants comments about *Ex parte Kranz*, said Board decision does not address EP 0180171 or the issue of whether EP 0180171 constitutes prior art.

8. Claims 1,2,6-8 stands rejected under 35 U.S.C. § 102(e) as being clearly anticipated by Pillai et al.

Pillai et al. teach in vivo administration of a conjugate containing Il-2 attached to a carbohydrate antigen (see column 3). The carbohydrate antigen is an antigen to which the host is previously sensitized (eg. one of the antigens disclosed in penultimate paragraph, column 3). While the reference does not disclose that the administration of the conjugate will lead to lysis of a target cell via the mechanism recited in the claim, said lysis will inherently occur because the claimed method recites the same steps as disclosed by Pillai et al. (eg. in vivo administration of the identical conjugate recited in the claims). Pillai et al. disclose that the conjugate is administered to a "warm blooded animal" (eg. mammal, see column 4, last paragraph).

Regarding applicants comments, the specification discloses that the selective member can encompass an antigen to which the host has been previously sensitized (see page 7, lines 25 and 26). Pillai et al. teach in vivo administration of a conjugate containing Il-2 attached to a carbohydrate antigen (see column 3) wherein the carbohydrate antigen is an antigen to which the host is previously sensitized (see column 3, last paragraph). There is no evidence of record that the antigens disclosed by Pillai et al. are not immunogenic. The list of carbohydrate antigens disclosed in Pillai et al. column 3, penultimate paragraph includes numerous antigens recognized in the art as immunogenic (eg. bacterial capsular polymers, LPS, allergens, tumor associated antigens, fungal and viral antigens) wherein it would be expected that antibodies would be present that bound said antigens in a variety of individuals. For example, virtually any individual would have antibodies against commonly encountered viral or bacterial or fungal antigens.

9. The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

10. Claim 4 remains rejected under 35 U.S.C. § 103 as being unpatentable over Pouletty (EP 0510949) in view of prior art disclosed in the specification (page 9, first complete paragraph) for the reasons elaborated in the previous Office Action. Applicants arguments have been considered and deemed not persuasive. Regarding applicants arguments, Pouletty teaches that the antigen used in the conjugate can be an antigen that binds naturally occurring antigens. α gal was known in the art as such an antigen.

11. Claims 1,7,8 are rejected under 35 U.S.C. § 103 as being unpatentable over Kranz et al. in view of Park et al. (US Patent 5,298,395).

Kranz et al. disclose the claimed method for lysing target cells wherein the conjugate used does not use an antibody as the "moiety specific for a surface protein" (see abstract and claims). Kranz et al. disclose use of a conjugate containing a growth factor as the "moiety specific for a surface protein" (see claims 27-31) and a "selective moiety" which is an antiT3 antibody (which binds the TCR). The claims under consideration do not exclude use of an antibody as the "selective moiety". Kranz et al. disclose the claimed method is used in vivo wherein lysis is mediated by T cells which bind said conjugate wherein the conjugate is bound by the appropriate target cell (see pages 3 and 4). Kranz et al. do not disclose use of a cytokine such as Il-2 as the "moiety specific for a surface protein". Kranz et al. disclose use of a conjugate containing a growth factor as the "moiety specific for a surface protein" (see claims 27-31). Park et al. disclose use of cytokines (eg. growth factors) in conjugates wherein the cytokine functions as a ligand for a receptor (see column 3, first complete paragraph). Park et al. disclose use of the cytokine IL-2 in such conjugates (see column 4, first complete paragraph). It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have created the claimed invention because Kranz et al. disclose the claimed method for lysing target cells wherein the conjugate used contains a growth factor as the "moiety specific for a surface protein" (see claims 27-31) and a "selective moiety" which is an antiT3 antibody (which binds the TCR), while Park et al. disclose use of cytokines (eg. growth factors) in conjugates wherein the cytokine functions as a ligand for a receptor. One of ordinary skill in the art would have been motivated to do the aforementioned because Kranz et al. disclose the claimed method for lysing target cells wherein the conjugate used contains a growth factor as the "moiety specific for a surface protein", while Park et al. disclose use of cytokines (eg. growth factors) in conjugates wherein the cytokine functions as a ligand for a receptor.

Regarding applicants comments, Kranz et al. disclose use of a conjugate containing a growth factor as the "moiety specific for a surface protein" (see claims 27-31). Park et al. disclose use of cytokines (eg. growth factors) in conjugates wherein the cytokine functions as a ligand for a receptor (see column 3, first complete paragraph). Park et al. disclose use of the cytokine IL-2 in such conjugates (see column 4, first complete paragraph).

12. No claim is allowed.

13. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

14. Papers related to this application may be submitted to Group 180 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Papers should be faxed to Group 180 at (703) 305-7939.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Ron Schwadron whose telephone number is (703) 308-4680. The examiner can normally be reached Monday through Thursday from 7:30 to 6:00. A message may be left on the examiners voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ms. Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1600 receptionist whose telephone number is (703) 308-0196.

RONALD B. SCHWADRON
PRIMARY EXAMINER
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Art Unit 1644